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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,280	04/26/2006	Takeshi Tabira	40072-0026US	3468

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,280	TABIRA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2010*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-29* is/are pending in the application.

4a) Of the above claim(s) *22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 04/22/2010 has been entered. No claim is amended.

This application 10/560,280 is a 371 of PCT/JP04/08224 06/11/2004 and claims benefit of foreign applications JAPAN 2003-169714 06/13/2003, JAPAN 2003-371103 filed on 10/30/2003.

Claims 1-18 are cancelled. Claims 19-29 are pending. Claims 22-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 19-21 and 29 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 19-21 and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Huston et al** (US 2005/0255113, publication date 11/17/2005, filed on 09/27/2004, continuation of 09/620,955 filed on 07/21/2000, provisional application 60/146,047, filed on 07/27/1999), issued on 10/14/2003, filed on 08/21/2000) in view of **Kuwako et al.** (Kuwako et al., Activation of calpain in cultured neurons overexpressing Alzheimer amyloid precursor protein, *Brain Res Mol Brain Res.* 107(2):166-75, 2002), **Milton et al.** (WO 2002/36614), and **Findeis et al.** (US

patent 5,854,204, issued on 12/29/1998). Applicant's arguments filed 04/22/2010 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 2-11 of the office action mailed on 01/22/2010.

For the clarity and completeness of this office action, previous rejection for the reasons of record advanced on pages 2-11 of the office action mailed on 01/22/2010, is reiterated below with editorial revisions for clarity of the rejection.

Claim 19 is directed to a method for treating Alzheimer's disease, comprising administering to a subject an adeno-associated virus vector which expresses β-amyloid peptide in intestinal cells in a therapeutically effective amount, wherein the adeno-associated virus vector comprises DNA encoding said β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form.

Claim 20 is directed to the method according to claim 19, wherein said β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2.

Claim 21 is directed to the method according to claim 19, wherein the DNA encoding said β amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1.

Claim 21 is directed to the method according to claims 19, said administering is orally administering.

Claim interpretation: The limitation "DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide" reads on the signal peptide located in the wild type N-terminal of amyloid precursor protein (APP). This interpretation is based on the disclosure in paragraph [0028] of specification, US 2009/0004144, publication of instant application.

Huston et al. teaches a method for inhibiting the formation of intracellular aggregates of a selected polypeptide in an animal by immunizing the animal, e.g., a human patient, with an immunogen having an epitope in common with the selected polypeptide, where the immunizing provokes a host antibody immune response sufficient for inhibiting the formation of aggregates, e.g., intracellular aggregates of the selected polypeptide from occurring. In a preferred embodiment, the immunogen is an expressible nucleic acid vaccine, e.g., a DNA vaccine, encoding a polypeptide comprising an epitope in common with a polypeptide such as, e.g., Amyloid Precursor Protein (See paragraph [0023], Huston et al. US 2005/0255113).

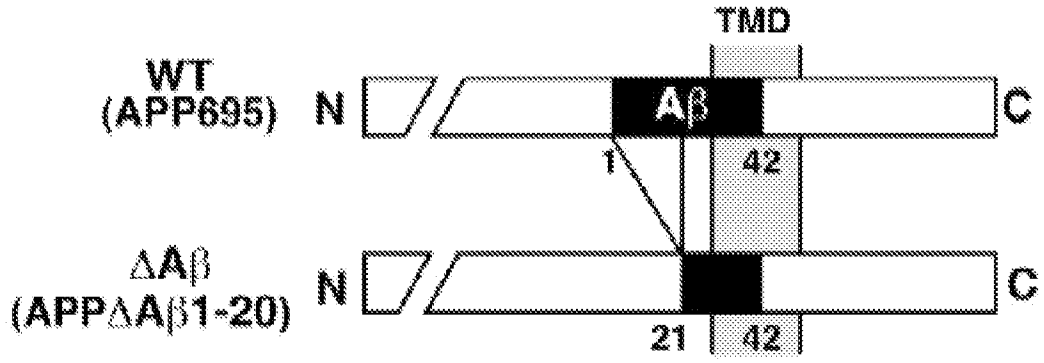
With regard to adeno-associated virus (AAV), Huston et al teaches expression vectors, such as viral vectors including adenoviruses and adeno-associated viruses), which serve equivalent functions (See paragraph [0125], Huston et al. US 2005/0255113).

With regard to orally administering AAV expressing β-amyloid peptide in intestinal cells recited in claim 19 and 29, Huston et al. teaches that the term "administering" refers to dispensing, delivering or applying the therapeutic agent to an animal or human by any suitable route for delivery of the therapeutic agent to the desired location in the animal or human, including delivery by either the parenteral or oral route, intramuscular injection, subcutaneous (intradermal) injection, intravenous injection, buccal administration, transdermal delivery, intracranial delivery, and administration by the intranasal or respiratory tract route. Huston et al teaches that the term "administering" is further intended to refer to bringing the therapeutic agent into close proximity with a cell, such that the therapeutic agent can exert its effects on the cell (See paragraph [0082], Huston et al. US 2005/0255113). It is noted that intestinal cells are cells exposed to and affected by the AAV vector recited in claim 19 of instant application is inherent

upon oral administration of adeno-associated viruses (AAV) vector taught by Huston et al. This interpretation is consistent with the notion that dependent claim 29 is further limiting claim 19.

Huston et al. does not explicitly teaches **(i)** the limitation "DNA encoding said β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form" recited in claim 19 of instant application, **(ii)** DNA encoding said β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, recited in claim 21 of instant application, and **(iii)** the limitation β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2 recited in claim 20 of instant application.

(i) With regard to the limitation "DNA encoding said β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form" recited in claim 19, **Kuwako et al.** teaches that Alzheimer's disease (AD) is a neurodegenerative disease and studies of the molecular mechanism of AD indicates that overexpression of wild-type amyloid precursor protein (APP) in postmitotic neurons induces cleavage-dependent activation of caspase-3 both in *vivo* and *in vitro* by recombinant adenovirus, which is an obvious variant of adeno-associated virus, expressing wild-type APP and its Aβ (1-20) lacking mutant (APPΔAβ20) (See abstract and material and Methods, Figure 1A, shown below, Kuwako et al., Activation of calpain in cultured neurons overexpressing Alzheimer amyloid precursor protein, *Brain Res Mol Brain Res.* 107(2):166-75, 2002).



It is noted that the limitation "DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide" reads on the signal peptide located in the wild type N-terminal of amyloid precursor protein (APP).

(ii) With regard to DNA encoding said β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1 recited in claim 21 of instant application, **Milton et al.** teaches amyloid-beta (Abeta) 1-43, its fragment capable of binding to the Aβ protein within the Aβ 1-43 region. The sequence alignment of the sequences of SEQ ID No: 1 with the sequences taught by Milton et al. is provided below, with bold sequences indicating nucleotide sequences 10-30 of SEQ ID NO: 1.

SEQ ID No: 1

```
RESULT 1
ABK52998
ID   ABK52998 standard; cDNA; 129 BP.
XX
AC   ABK52998;
XX
DT   21-AUG-2002  (first entry)
XX
DE   Human cDNA encoding amyloid beta peptide 1-43.
XX
KW   Human; ss; amyloid beta 1-43; Alzheimer's disease; antisense peptide;
KW   cyclin dependent kinase; nootropic; Abeta; phosphorylation; vaccine;
KW   neuroprotective; catalase; p34-cdc22.
XX
```

OS Homo sapiens.
XX
FH Key Location/Qualifiers
FT CDS 1. .129
FT /*tag= a
FT /product= "Amyloid beta 1-43"
FT /partial
FT /note= "No start or stop codon shown"
XX
PN **WO200236614**-A2.
XX
PD 10-MAY-2002.
XX
PF 01-NOV-2001; 2001WO-GB004843.
XX
PR 01-NOV-2000; 2000GB-00026738.
PR 01-NOV-2000; 2000GB-00026739.
XX
PA (INSI-) INSIGHT BIOTECHNOLOGY LTD.
XX
PI **Milton** NGN;
XX
DR WPI; 2002-490001/52.
DR P-PSDB; AAU98701.
XX
PT New antisense peptides of amyloid beta protein residues 1-32, useful for
PT detecting, preventing and treating Alzheimer's disease, or for
PT identifying therapeutic agents that prevent cytotoxicity or
PT phosphorylation of amyloid beta.
XX
PS Disclosure; Fig 1; 44pp; English.
XX
CC The invention relates to a peptide (I) comprising the antisense sequence
CC of amyloid-beta (Abeta) 1-43, its fragment capable of binding to the
CC Abeta protein within the Abeta 1-43 region, or a homologue of the peptide
CC or fragment having the same hydropathic profile or at least 60% sequence
CC identity. Also included are (1) a phosphorylated Abeta protein or its
CC fragment for use in therapy; (2) an isolated recombinant vector
CC comprising a polynucleotide encoding (I); (3) an antibody raised against
CC (I) (including an antibody having no or reduced affinity for the non-
CC phosphorylated form of the protein and an antibody raised against the
CC peptides appearing as AAU98708-AAU98716); (5) determining if a patient is
CC at risk for Alzheimer's disease by analysing a sample from the patient
CC that contains Abeta to determine if Abeta is phosphorylated, where
CC phosphorylation indicates a risk of Alzheimer's disease; (6) an assay for
CC identifying an agent that inhibits the interaction of Abeta protein with
CC other protein by contacting Abeta protein or its fragment with a target
CC agent and a peptide that binds to Abeta (or fragment), and determining if
CC the agent inhibits the peptide from binding to Abeta compared to a
CC control assay carried out in the absence of the peptide; (7) an assay for
CC identifying an agent that binds to Abeta within the region Abeta 1-43, by
CC contacting a target agent with a peptide as defined above, and
CC determining if the agent binds to the peptide; and (10) a compound that
CC blocks the activity of a phosphorylated Abeta protein. The antisense
CC peptide is useful in therapy, and in the manufacture of a medicament for
CC therapy of a condition mediated by phosphorylation of Abeta or by binding
CC of endogenous Abeta to catalase, where such condition is Alzheimer's
CC disease. The peptide comprising the amino acid sequence Abeta 1-43 or its
CC fragment capable of binding to cyclin-dependent kinase is useful in the
CC manufacture of a medicament for therapy of a condition mediated by

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CC   phosphorylation of Abeta. The protein kinase inhibitor may be used in the
CC   manufacture of a medicament for treating Alzheimer's disease, where the
CC   inhibitor selectively binds to where protein and the kinase is p34-cdc22.
CC   The antisense peptides may also be used for detecting, preventing and
CC   treating Alzheimer's disease, for identifying therapeutic agents that
CC   prevent Abeta cytotoxicity or phosphorylation of Abeta, and in vaccines.
CC   A phosphorylated Abeta fragment may be used to generate antibodies
CC   specific for the phosphorylated form, or as an antigen in a vaccine
CC   composition. The present sequence encodes Abeta 1-43
XX
SQ   Sequence 129 BP; 38 A; 21 C; 35 G; 35 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 129;  DB 1;  Length 129;
  Best Local Similarity   100.0%;
  Matches  129;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATGCAGAATTCCGACATGACTCAGGATATGAAGTTCATCATCAAAAATTGGTGTTCTTT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GATGCAGAATTCCGACATGACTCAGGATATGAAGTTCATCATCAAAAATTGGTGTTCTTT 60

Qy         61 GCAGAAGATGTGGGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGGCGGTGTTGTC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GCAGAAGATGTGGGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGGCGGTGTTGTC 120

Qy        121 ATAGCGACA 129
              |||||||||
Db        121 ATAGCGACA 129
```

(iii) With regard to the limitation β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2 recited in claim 20 of instant application, **Findeis et al.** teaches β-amyloid peptide (βAP) derivatives, and the βAP derivatives inhibit aggregation of amyloidogenic proteins. The sequence alignment of the sequences of SEQ ID No: 2 with the sequences taught by Findeis et al. are provided below, with bold sequences indicating amino acids 4 to 10 of SEQ ID NO: 2.

SEQ ID No: 2

```
RESULT 14
AAW89362
ID   AAW89362 standard; peptide; 43 AA.
XX
AC   AAW89362;
XX
DT   02-MAR-1999  (first entry)
XX
DE   Beta-amyloid peptide derivative A-beta-1-43.
```

XX
KW Human; beta-amyloid peptide; Alzheimer's disease; amyloidogenic protein;
KW aggregation; neurotoxicity; amyloidosis; Down's syndrome; cardiomyopathy;
KW familial amyloid polyneuropathy; bovine spongiform encephalopathy;
KW Creutzfeldt-Jakob disease; bAP.
XX
OS Homo sapiens.
OS Synthetic.
XX
PN US**5854204**-A.
XX
PD 29-DEC-1998.
XX
PF 14-MAR-1996; 96US-00612785.
XX
PR 14-MAR-1995; 95US-00404831.
PR 07-JUN-1995; 95US-00475579.
PR 27-OCT-1995; 95US-00548998.
XX
PA (PRAE-) PRAECIS PHARM INC.
XX
PI Hundal A, Gefter ML, Kasman L, Musso G, Molineaux S, Benjamin H;
PI **Findeis** MA, Chin J, Lee J, Kelley M, Reed M, Wakefield J;
PI Garnick MB, Kubasek W, Signer ER;
XX
DR WPI; 1999-094964/08.
XX
PT New peptide(s) derived from beta-amyloid peptide that inhibit amyloid
PT aggregation - and neurotoxicity, specifically for treatment and
PT prevention of Alzheimer's disease.
XX
PS Example 1; Col 46; 52pp; English.
XX
CC The present invention describes beta-amyloid peptide (bAP) derivatives.
CC The bAP derivatives inhibit aggregation of amyloidogenic proteins and
CC peptides, specifically bAP, and their neurotoxicity, so are useful for
CC treating and preventing any disease involving amyloidosis, specifically
CC Alzheimer's disease but also Down's syndrome, familial amyloid
CC polyneuropathy or cardiomyopathy, bovine spongiform encephalopathy and
CC Creutzfeldt-Jakob disease. The bAP derivatives are also used to diagnose
CC these diseases, in vitro or in vivo, by detecting binding of bAP to
CC labelled bAP derivatives. Some bAP derivatives inhibit bAP aggregation
CC even when bAP is present in molar excess. The present sequence represents
CC a bAP derivative
XX
SQ Sequence 43 AA;

Query Match 100.0%; Score 222; DB 1; Length 43;
Best Local Similarity 100.0%;
Matches 43; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 DAE**FRHDSGY**EVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT 43
||||||||||||||||||||||||||||||||||||||||||
Db 1 DAE**FRHDSGY**EVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT 43

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Huston et al. regarding a method for inhibiting the formation of intracellular aggregates of a selected polypeptide in an animal by immunizing the animal, e.g., a human patient, with an immunogen having an epitope in common with the selected polypeptide, where the immunizing provokes a host antibody immune response sufficient for inhibiting the formation of aggregates, e.g., intracellular aggregates of the selected polypeptide from occurring, wherein the immunogen is an expressible nucleic acid vaccine, e.g., a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), via oral administration of AAV vector to intestinal cells, with the teachings of (i) Kuwako et al. regarding Alzheimer's disease (AD) is a neurodegenerative disease and studies of the molecular mechanism of AD indicates that overexpression of wild-type amyloid precursor protein (APP) in postmitotic neurons induces cleavage-dependent activation of caspase-3 both in *vivo* and *in vitro* by recombinant adenovirus, which is an obvious variant of adeno-associated virus, expressing wild-type APP and its Aβ (1-20) lacking mutant (APPΔAβ20), (ii) Milton et al. regarding amyloid-β (Aβ) 1-43, its fragment capable of binding to the Aβ protein within the Aβ 1-43 region, and β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and (iii) Findeis et al. regarding β-amyloid peptide (βAP) derivatives, and the βAP derivatives inhibit aggregation of amyloidogenic proteins, and the amino acid sequence alignment of SEQ ID No: 2 with the sequences taught by Findeis et al., to arrive at the claimed methods recited in claims 19-21 and 29 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Huston et al. with the teachings of Kuwako et al., Milton et al., and Findeis et al. because (i)

Huston et al. teaches that the immunization of a subject with a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of a polypeptide comprising an epitope of amyloid precursor protein (APP), (ii) Kuwako et al. teaches construction of adenovirus vectors expressing wild-type APP and APPΔAβ20 for analysis of molecular events linked to Alzheimer's disease, (iii) Milton et al. teaches β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and (iv) Findeis et al. teaches β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2.

There would have been a reasonable expectation of success given (i) the disclosure of the immunization of a subject with a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of a polypeptide comprising an epitope of amyloid precursor protein (APP), and the *in vivo* demonstration of a nucleic acid vaccine for eliciting a therapeutic host antibody immune response against undesired pathogenic intracellular huntingtin polypeptide complexes, by the teachings of Huston et al. (See Example 8, Huston et al.), (ii) the successful demonstration of the construction of adenovirus vectors expressing wild-type APP and APPΔAβ20 for analysis of molecular events linked to Alzheimer's disease, by the teachings of Kuwako et al., and (iii) the disclosure at nucleotide and amino acid levels regarding β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2, by the teachings of Milton et al. and Findeis et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that Huston et al. fails to disclose or suggest an adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and "DNA encoding a signal peptide." The APP secreted by the DNA vaccine of Huston et al. is a different antigen from the Aβ peptide itself. APP generates AI3 peptide when partially decomposed by enzymes in neural cells (see paragraph 0002, lines 6 to 8 of the present specification). Applicant argues that, further, Huston et al. fails to disclose or suggest that the adeno-associated virus vector expressing AI3 peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Huston et al. fails to disclose or suggest that the adeno-associated virus vector expressing AI3 peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Applicant argues that Kuwako et al. fails to disclose or suggest an adeno-associated virus vector comprising "DNA encoding AI3 peptide" itself and "DNA encoding a signal peptide." Further, Kuwako et al. fails to disclose or suggest that adeno-associated virus vector expressing AI3 peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Kuwako et al. fails to disclose or suggest that an adeno-associated virus vector expressing AI3 peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Applicant argues that Milton et al. fails to disclose or suggest an adeno-associated virus vector comprising "DNA encoding Aβ peptide" itself and "DNA encoding a signal peptide." Further, Milton et al. fails to disclose or suggest that an adeno-associated virus vector expressing Aβ peptide in intestinal cells remarkably reduces intracellular and extracellular amyloid plaques. Also, Milton et al. fails to disclose or suggest that adeno-associated virus vector expressing Aβ peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Applicant argues that Findeis et al. fails to disclose or suggest that an adeno-associated virus vector comprising "DNA encoding AI3 peptide" itself and the "DNA encoding a signal peptide." Further, Findeis et al. fails to disclose or suggest that an adeno-associated virus vector expressing AI3 peptide in intestinal cells remarkably reduces intracellular and extracellular

amyloid plaques. Also, Findeis et al. fails to disclose or teach that an adeno-associated virus vector expressing Aβ peptide in intestinal cells reduces the concentration of TGF-β in the blood.

Applicant argues that the claimed invention is not rendered obvious by the cited art. In addition, the present invention has led to ALZHEIMER'S DISEASE AWARD, 2005 presented by the Journal of Alzheimer's disease (see http://www.j-alz.com/award/award_2005.html). Applicant states that this award further indicates that one skilled in the art considers the present invention unexpected and remarkable.

Response to Applicant's arguments

Applicant is reminded that this maintained rejection is a 103 rejection, not a 102(e) rejection anticipated by Huston et al. In this regard, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The maintained 103 rejection has clearly documented the following statements:

"Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Huston et al. regarding a method for inhibiting the formation of intracellular aggregates of a selected polypeptide in an animal by immunizing the animal, e.g., a human patient, with an immunogen having an epitope in common with the selected polypeptide, where the immunizing provokes a host antibody immune response sufficient for inhibiting the formation of aggregates, e.g., intracellular aggregates of the selected polypeptide from occurring, wherein the immunogen is an expressible nucleic acid vaccine, e.g., a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), via oral administration of AAV vector to intestinal cells, with the teachings of (i) Kuwako et al. regarding Alzheimer's disease (AD) is a neurodegenerative disease and studies of the molecular mechanism of AD indicates that overexpression of wild-type amyloid precursor protein (APP) in postmitotic neurons induces cleavage-dependent activation of caspase-3 both in *vivo* and *in vitro* by recombinant adenovirus, which is an obvious variant of adeno-associated virus, expressing wild-type APP and its Aβ (1-20) lacking mutant (APPΔAβ20), (ii) Milton et al.

regarding amyloid-β (Aβ) 1-43, its fragment capable of binding to the Aβ protein within the Aβ 1-43 region, and β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and (iii) Findeis et al. regarding β-amyloid peptide (βAP) derivatives, and the βAP derivatives inhibit aggregation of amyloidogenic proteins, and the amino acid sequence alignment of SEQ ID No: 2 with the sequences taught by Findeis et al., to arrive at the claimed methods recited in claims 19-21 and 29 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Huston et al. with the teachings of Kuwako et al., Milton et al., and Findeis et al. because (i) Huston et al. teaches that the immunization of a subject with a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of a polypeptide comprising an epitope of amyloid precursor protein (APP), (ii) Kuwako et al. teaches construction of adenovirus vectors expressing wild-type APP and APPΔAβ20 for analysis of molecular events linked to Alzheimer's disease, (iii) Milton et al. teaches β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and (iv) Findeis et al. teaches β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2.

There would have been a reasonable expectation of success given (i) the disclosure of the immunization of a subject with a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of a polypeptide comprising an epitope of amyloid precursor protein (APP), and the *in vivo* demonstration of a nucleic acid vaccine for eliciting a therapeutic host antibody immune response against undesired pathogenic intracellular huntingtin polypeptide complexes, by the teachings of Huston et al. (See Example 8, Huston et al.), (ii) the successful demonstration of the construction of adenovirus vectors expressing wild-type APP and APPΔAβ20 for analysis of molecular events linked to Alzheimer's disease, by the teachings of Kuwako et al., and (iii) the disclosure at nucleotide and amino acid levels regarding β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in

SEQ ID NO: 1, and β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2, by the teachings of Milton et al. and Findeis et al."

It is worth noting that claims 19-21 and 29 do not require any specific limitation pertaining to "reduces the concentration of TGF-β in the blood" as Applicant argues the non-obviousness of the claimed methods for treating Alzheimer's disease. Furthermore, it is noted that the argument regarding "ALZHEIMER'S DISEASE AWARD, 2005 presented by the Journal of Alzheimer's disease" to the inventors has no bearing on the patentability to the claimed methods. As a related issue, Applicant fails to provide any evidence in what aspect(s) the claimed methods are considered as "unexpected" because Applicant merely asserts that "one skilled in the art considers the present invention unexpected and remarkable".

With regard to asserted requirement for teaching/suggestion/motivation, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine the teachings of Huston et al., Kuwako et al., Milton et al., and Findeis et al. has been clearly documented above in this office action.

Conclusion

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

3. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632